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NDA 20-766

FEB 1 1999

Hoffman-La Roche Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

We acknowledge receipt on January 19, 1999, of your January 18, 1999, resubmission to your new drug application (NDA) for Xenical (orlistat) Capsules.

This resubmission, submitted in response to our May 12, 1998, action letter, contains revised labeling and the data from a randomized, double-blind, placebo-controlled, parallel-group clinical study to support a conclusion that orlistat does not increase the risk of breast cancer. We also acknowledge your request for a waiver of the required establishment re-inspection; that request has been forwarded to the appropriate office for a decision.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is July 19, 1999.

If you have any questions, contact Maureen Hess, Project Manager, at (301) 827-6411.

Sincerely yours,

/S/ [redacted] 2.1.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:Archival NDA 20-766
HFD-510/Div. Files
HFD-510/E.Galliers/MHess/SSobel
HFD-510/Reviewers/TeamLeaders
HFD-102/FHoun/JBilstad
DISTRICT OFFICE

Drafted by: emg/February 1, 1999 \filename: 20766RS2.AC

ACKNOWLEDGEMENT (AC)

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NDA 20-766

Hoffmann-La Roche Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

SEP 28 1998

Dear Ms. Jack:

Reference is made to your New Drug Application (NDA) for Xenical (orlistat) Capsules, which received an approvable letter on May 12, 1998.

The Division has reviewed your submission dated August 11, 1998, which outlines a proposal for auditing the sites of the European Phase 3b program. Although we are interested in reviewing the results of your internal audit, we plan to proceed with our own audit, which, as previously discussed, will most likely focus on breast cancer safety data.

Accordingly, please submit the following to the NDA within three weeks so that we may begin to plan and prepare our audit of the Phase 3b program:

1. Names and complete addresses of the principal investigators.
2. Number of patients treated by each investigator.
3. Identification of all patients with a breast cancer diagnosis.

In addition, we request that one copy of this information be submitted as a desk copy.

We appreciate your cooperation.

Should you have any questions regarding this communication, please contact Maureen Hess, MPH, RD at (301) 827-6411.

Sincerely yours,

/S/ 9/25/98

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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NDA 20-766

NOV 19 1997

Hoffmann-La Roche Inc.
Attention: Ms. Peggy Jack
Program Coordinator
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xenical (orlistat)

Therapeutic Classification: Priority

Date of resubmitted Application: November 14, 1997

Date of Receipt: November 17, 1997

Our Reference Number: 20-766

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 16, 1998, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Maureen Hess, MPH, RD
Consumer Safety Officer
Telephone: (301) 827-6411

Please cite the NDA number listed above at the top of the first page of any communications

concerning this application.

Sincerely yours,

/S/ 11/19/97

Enid Galliers
Chief, Project Managment Staff
Division of Metabolic and Endocrine Drug Products
(HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

HESS

NDA 20-766

OCT 10 1997

Hoffmann-La Roche Inc.
Attention: Ms. Peggy Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

The Division has given careful consideration to your September 30, 1997 request for a meeting to discuss issues related to the re-submission of Xenical (orlistat), NDA 20-766.

At the time of the NDA withdrawal the Division had serious concerns about the finding of an increased incidence of breast cancer in women treated with orlistat compared with control subjects. In response to our concern, Roche initiated a breast cancer follow-up survey of women who participated in the phase 3 clinical trials. It is our understanding that the final study report from this follow-up survey will form the nucleus of the re-submission, as these data are the most relevant to our concern about Xenical. After the Division receives the re-submission and the review process has been initiated we will be in a position to discuss details about the review process itself, including the potential involvement of oncology experts and the need for an advisory committee meeting. Until such time, however, it seems premature to schedule a meeting with your proposed agenda.

If you have any questions regarding this communication, please contact Maureen Hess, MPH, RD at (301) 827-6411.

Sincerely yours,

/S/ [redacted] 10/10/97

Solomon Sobel, M.D.
Director
Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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NDA 20-766

OCT 2 1997

Hofffmann-La Roche Inc.
Attention: Peggy Jack
Program Director
340 Kingsland St.
Nutley, NJ 07110

Dear Ms. Jack:

Reference is made to your New Drug Application (NDA) for Xenical (orlistat) Capsules. The Division has reviewed the protocol submitted August 27, 1997, entitled, "Weight reducing and NIDDM preventing effects of Xenical in obese patients," (The Swedish Study) and here within provide comment.

The primary objective of the Swedish Study is to determine if Xenical, as compared with placebo, can reduce impairment of glucose tolerance and decrease the incidence of NIDDM in obese patients with normal or impaired glucose tolerance at baseline. It is anticipated that approximately 3,000 patients, of which 1,800 will be obese women between 30 and 60 years of age will be randomized into this 2-year study. Women with a history of cancer (including breast cancer) will be excluded from participating in the study. Mammograms will be obtained at baseline and only those women with mammograms read as normal or as having "benign changes" will be enrolled into the study. Follow-up mammograms will be obtained after one and two years of treatment.

Given the possibility that Xenical *may* act as a tumor promoter, a concern raised by the finding of an increased incidence of breast cancer in Xenical-vs placebo-treated patients, we agree with the decision to incorporate mammographic evaluation into the study. However, the ethical necessity of excluding women with abnormal baseline mammograms- and thus studying lower-risk women- will in all probability, diminish the ability to draw meaningful conclusions about Xenical's potential as a breast cancer promoter. Increasing the size and duration of the study may further alleviate studying low-risk women. In any event, we cannot at this point, state with certainty how the data will affect the approvability and/or labeling.

If you have any questions concerning this communication, please contact:

Maureen Hess, MPH, RD
Consumer Safety Officer
(301) 827-6411

Sincerely yours,

/S/ [redacted] for 10-2-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

HESS

NDA 20-766

MAY 27 1997

Hoffmann-La Roche
Attention: Peggy Jack
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Jack:

We acknowledge receipt on May 27, 1997 of your May 23, 1997 amendment to your new drug application for Xenical (orlistat) Capsules.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is August 27, 1997.

If you have any questions, please contact Maureen Hess, MPH, RD, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

/S/ [redacted] 5-27-97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

HESS

NDA 20-766

MAY 19 1997

Hoffmann-La Roche
Attention: Mr. Don Cooper
340 Kingsland Street
Nutley, NJ 07110

Dear Mr. Cooper:

During the teleconference scheduled for May 19, 1997, we will be requesting the following information:

A. Identification of all studies and case reports by study number and case report number, respectively.

B. Presentation of data in four groupings.

1. Completed randomized clinical trials (RCT)
2. Other completed studies
3. Ongoing randomized clinical trials
4. Other ongoing studies

C. Randomized clinical trials should include the following:

1. N randomized, by treatment group
2. Scheduled duration of trial
3. N completing scheduled duration, by treatment group
4. If applicable, N re-randomized by treatment group, scheduled duration of trial, and N completing scheduled duration by treatment group

D. For other studies, please provide:

1. N enrolled, by treatment group
2. Scheduled duration of study
3. N completing scheduled duration, by treatment group

E. Case reports for all cases of breast cancer known to have been diagnosed during the scheduled duration of an RCT or other study, including cases diagnosed on study drug and cases diagnosed off study drug, with the following information:

1. Type of study (RCT, other) and treatment group

2. Number of days on study drug and number of days off study drug at time of diagnosis
3. Tumor site, size and histopathology
4. Characteristics of patient: age, ethnic group, family and personal medical history, etc.

F. Case reports for all other cases of breast cancer known to have been diagnosed in women who had used orlistat.

Please limit all data to women. Thank you for your cooperation. If you have any questions, please contact, Maureen Hess, MPH, RD at (301) 443-3510.

Sincerely,

/S/ [redacted] 5/16/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL